

REVIEW ON ENHANCEMENT OF GLUCOSE UPTAKE AND UP-REGULATION OF GLUCOSE TRANSPORTERS BY ANTIDIABETIC MEDICINAL PLANTS

GAYATHRI GA, GAYATHRI MAHALINGAM*

Division of Industrial Biotechnology, School of Bio Sciences and Technology, VIT University, Vellore - 632 014, Tamil Nadu, India.

Email: gayathrigopinath@vit.ac.in

Received: 08 January 2016, Revised and Accepted: 21 January 2016

ABSTRACT

Glucose is a key fuel in mammalian cells that import by a process of facilitative diffusion mediated by glucose transporters (GLUT). A defect in GLUT expression for prolong time leads to diabetes mellitus. Medicinal plants used in traditional treatments confirm a possibility of tackling diabetes by regulating the GLUT activity in the body, with lesser side effects. Resistant of tissues to insulin is a major manifestation in type 2, and the cause can be localized in defect of glucose that can be reverse by medicinal plants. *In vitro*, *in vivo*, and *in silico* studies of plant extracts and its active compounds support for their multiple target mechanisms. Many medicinal plants used in the traditional medicine enhancing the translocation of GLUT and this could lead to a new approach for treating type 2 diabetes.

Keywords: Diabetes, Glucose transporters, Mechanism of glucose transporter, Glucose transporters 4, Medicinal plants.

INTRODUCTION

Since diabetes is a multifactorial disease leading to several complications, it demands multiple therapeutic approaches. Present oral therapeutics available for the treatment of type 2 diabetes mellitus (T2DM) has a single active constituent and target for specific mechanisms to act on [1]. However, there are certain limitations to these synthetic drugs due to their high cost and side effects [2,3]. Long back from *Sushruta samhita* medicinal plants are conserved as an esteemed source of drugs and becoming a growing part of modern hi-tech medicine. In contrast to synthetic drugs, herbal medications can target multiple mechanisms [4]. The medicinal plants being studied have varied mechanisms of action like:

- a. Lowering blood glucose level [5]
- b. Increasing anti-inflammatory response [6]
- c. Reducing oxidative damages [7]
- d. Insulin-mimetic agents and insulin-secretagogues [8]
- e. Improving insulin resistance and glucose tolerance [9]
- f. Up-regulation of glucose uptake [10]
- g. Inhibiting protein activity [11]
- h. Activating various signaling pathways in the body and increasing the glucose transporter (GLUT) activity [12].

Many of the medicinal plants discussed help to improve GLUT activity in the body. Thus, the GLUTs from the plants are considered as most attractive targets for drug development [13]. The present article provides a comprehensive review on the antidiabetic plants that have been proved by the mechanism of action through GLUTs.

DIABETES AND GLUTS

The exploration of the role of GLUTs in diabetes is an area that is likely to produce considerable future advances. The detailed studies in rodents and human subjects revealed the significance of isoforms GLUT2, GLUT4 in peripheral insulin action [14], and regulation of whole-body glucose homeostasis. The failure of GLUT4 expression would represent a significant advance in the development of symptoms of diabetes. In type 2 diabetes patients, depleted the intracellular pool of GLUTs in adipose tissue has been identified [15]. Insulin resistance and diabetic conditions suggest that defective glucose transport in muscle may result from impaired translocation of GLUT4. These defects can be solved by other factors such as phosphatase inhibitors, exercise, and hypoxia.

Stimulation of insulin receptor substrate-1 (IRS-1) phosphorylation and PI3 kinase activity in T2DM and, insulin-resistant states may contribute for the enhancement in GLUT4 translocation.

EFFECTS OF MEDICINAL PLANTS AND ITS ACTIVE CONSTITUENTS ON GLUT MECHANISM

After digestion, glucose uptake by peripheral tissues is one of the multiple mechanisms, which maintain blood glucose level in the body. Glucose uptake process involved in the activation of the GLUT in the liver, adipocytes, and skeletal muscle cells. Medicinal plants or their active constituents that can up-regulate GLUT expression and translocation that helps in the treatment of insulin resistance and hyperglycemia. Evidence from insulin-resistant rodent models suggests that defective glucose transport in muscle may result from impaired translocation of GLUT4 that can be effectively alleviated by conventional therapy. Hence, targeting this is the most gold promising goal for the treatment of type DM. This review provides the information on up-regulation of GLUT translocation by the isolated compounds and its medicinal plants which may help the researchers involved in this field to explore the mechanism of action unexplored medicinal plants.

ISOLATED ACTIVE PRINCIPLES AND CRUDE EXTRACT FROM MEDICINAL PLANTS ENHANCE GLUT ACTIVITY

Many medicinal plants studied have involved in the activation of PI3 kinase and subsequent phosphorylation and resulting in GLUT4 translocation. Some of the medicinal plants or its active compounds can enhance glucose uptake and up-regulation of GLUTs are discussed below.

CINNAMALDEHYDE (CND)

Bioassay-guided fractionation of chloroform extract of *Cinnamomum zeylanicum* has performed by Anand *et al.*, in 2010, and identified CND as an active principle against diabetes. Oral administration of CND to diabetic rats for 2 months showed significant improvement in muscle and hepatic glycogen content. *In vitro* incubation of pancreatic islets with CND enhanced the insulin release compared to glibenclamide. The insulinotropic effect of CND was found to increase the glucose uptake through GLUT4 translocation in peripheral tissues. The treatment also showed a significant improvement in altered enzyme activities of pyruvate kinase and phosphoenolpyruvate carboxykinase and their messenger RNA (mRNA) expression levels [16].

CND on GLUT4 gene expression in C2C12 skeletal muscle cells using real-time polymerase chain reaction (PCR) was done by Nikzamir *et al.* in 2014. In this, a significant increase in the expression of GLUT4 in CND treated cells was observed and thus supports for its previous study [17].

GALLIC ACID (GA)

Vishnu Prasad *et al.*, in 2009, have identified and functionally characterized GA as the active principle from sea buckthorn leaf extract that increases glucose uptake in 3T3-L1 adipocytes. GA stimulates glucose uptake by inducing GLUT4 translocation in a wortmannin-sensitive but Akt-independent manner via atypical protein kinase C ζ/λ [18].

PLUMBAGIN

Plumbago zeylanica L. root is widely used in the traditional Indian medicine to treat DM. Plumbagin was isolated by Christudas Sunil *et al.* to explore their antidiabetic activity through glucose transporting mechanism. 15 and 30 mg/kg bwt of plumbagin were orally administered to streptozotocin-induced diabetic rats for 28 days. The compound significantly reduced the blood glucose and also altered all other biochemical parameters to normal. After treatment with plumbagin, enhanced GLUT4 mRNA and protein expression were observed in diabetic rats. In addition to this, it increased the activity of hexokinase and decreased the activities of glucose-6-phosphatase and fructose-1, 6-bisphosphatase significantly in treated diabetic rats. The results indicated that plumbagin enhanced GLUT4 translocation and contributed to glucose homeostasis [19].

CHEMICAL CONSTITUENTS FROM EUCALYPTUS CITRIODORA HOOK LEAVES

Wang *et al.* isolated compounds from *E. citriodora* to evaluate its ability to translocate GLUT4. *In vitro* cell-based GLUT4 translocation assay using stable L6 cells expressing pIRAP-m orange cDNAs was performed. In this, betulinic acid and corosolic acid were the most active compounds, displaying 2.38- and 1.78-folds GLUT4 translocation enhancement, respectively. The tripenes oleanolic acid, ursolic acid, madasiatic acid, and euscaphic acid, exhibited moderate GLUT4 translocation activity with 0.70-1.06 folds [20].

4-HYDROXYPIPECOLIC ACID (4-HPA)

4-HPA, isolated from the seed of *P. harmala* by G. Naresh in 2012. Effect of 4-HPA on glucose uptake and GLUT4 translocation was investigated in L6 skeletal muscle cell lines. Treatment with 4-HPA stimulated both glucose uptake and GLUT4 translocation from intracellular to the plasma membrane in skeletal muscle cells in a concentration-dependent manner. These observations support that 4-HPA stimulate GLUT4 translocation through PI-3-Kinase-mediated insulin signaling pathway [21].

NARINGENIN

Zygmunt *et al.*, in 2010, reported that Naringenin stimulated glucose uptake in L6 myotubes in a dose- and time-dependent manner. It correlated with insulin in glucose uptake and did not increase glucose uptake in myoblasts. This result indicating that GLUT4 GLUTs may be involved in the naringenin-stimulated glucose uptake and suggested that naringenin increases glucose uptake by skeletal muscle cells in an AMP-activated protein kinase (AMPK)-dependent manner [22].

BERBERINE

Berberine, an isoquinoline alkaloid isolated from some Chinese medicinal herbs such as *Coptidis Rhizoma* and *Cortex Phellodendri* (So Hui KIM *et al.*). The treatment of berberine to 3T3-L1 adipocytes enhanced basal glucose uptake was noted in normal and in insulin-resistant state. Inhibition of phosphatidylinositol 3-kinase by the inhibitor wortmannin not disturbed the effect on basal glucose uptake and the expression of GLUT1 in 3T3-L1 treated cells. Moreover, berberine treatment increased AMPK activity in 3T3-L1 cells [23].

CATECHIN

Catechin isolated from methanolic stem extract of *Cassia fistula* which is used in the Indian medicine to treat diabetes. The mRNA expression of GLUT4 and protein was enhanced in skeletal muscle of diabetic rats. This stud correlates with Docking study in Discovery Studio 2.1 shows the hypoglycemic effect and activates IR with peroxisome proliferator-activated receptor-gamma (PPAR γ) [24].

VANADATE AND TRIGONELLA

Immunoblotting and immunohistochemistry studies showed that the treatment of diabetic rats with combined doses of vanadate and *Trigonella* seed powder are most effective in the plasma glucose homeostasis and enhances the GLUT4 expression in skeletal muscle [25].

EMBELIN

Embelin was isolated from *Embelia ribes* significantly increased the PPAR γ expression in epididymal adipose tissue compared to diabetic control group and inhibited adipogenic activity. It moderately activates PPAR γ levels in the liver and skeletal muscle and also regulated insulin-mediated glucose uptake in epididymal adipose tissue through translocation and activation of GLUT4 in PI3K/p-Akt signaling cascade [26].

EPICATECHIN (EC) AND COCOA PHENOLIC EXTRACT (CPE)

Both enhanced the tyrosine phosphorylation and total IR, IRS-1 and IRS-2 levels, and activated the PI3K/AKT pathway and AMPK in HepG2 cells. Phenolic extract of Coca enhanced the levels of GLUT2. EC and CPE enhanced the tyrosine phosphorylation and total IR, IRS-1 and IRS-2 levels, and activated the PI3K/AKT pathway and AMPK in HepG2 cells. CPE also enhanced the levels of GLUT2. In addition, EC- and CPE-regulated hepatic gluconeogenesis was prevented by the blockage of AKT and AMPK [27].

GINSENSIDE RH2

Panax ginseng is a potential antidiabetic medicinal plant. Ginsenoside Rh2 increases the gene expression of GLUT4, at the mRNA and protein levels, in soleus muscle obtained from STZ-diabetic rats as a result of the increased β -endorphin secretion [28].

TINOSPORA CORDIFOLIA AND ITS COMPOUND PALMITINE

T. cordifolia is a well-investigated antidiabetic plant used in the Indian traditional medicine and also possessing several medicinal values. Sangeetha *et al.*, in 2013, studied the mechanism of action of *T. cordifolia* and its active compound palmitine in differentiated myocytes, L6 cells which can enhance GLUT4 up to 5- and 4-fold, respectively and up-regulates PPAR γ 0.67- and 0.38-fold. Further, the inhibitors of insulin pathway prevented glucose uptake mediated by *T. cordifolia* and palmitine which shows that the activity is majorly facilitated through insulin pathway [29].

AEGLES MARMELOS AND SYZYGIIUM CUMINI

A. marmelos and *S. cumini* are antidiabetic medicinal plants being used in the Indian traditional medicine. The dried powder was extracted sequentially using different organic solvents in increasing order of polarity and was analyzed for glucose uptake activity at each step. Methanol extracts were found to be significantly active at 100 ng/ml dose comparable with insulin and rosiglitazone. Elevation of GLUT4, PPAR γ , and PI3 kinase by these plants supported the up-regulation of glucose uptake. Hence, it was concluded that methanolic extracts of *A. marmelos* and *S. cumini* activate glucose transport in a PI3 kinase-dependent fashion [30].

ALLIUM SATIVUM, ALLIUM ASCALONICUM, SALVIA OFFICINALIS

A. sativum (Garlic), *A. ascalonicum* (Persian shallot), and *S. officinalis* (Sage) have been used traditionally as antidiabetic herbal medicines.

An antidiabetic effect of methanolic extracts of the above mentioned three plants on alloxan diabetic rats was investigated. After 3 weeks of treatment by methanolic plant extracts, increased expression of insulin and GLUT4 genes in diabetic rats treated with these plants extracts was observed. *S. officinalis* reduced blood glucose in a similar way as acarbose and also intestinal sucrase and maltase activities were inhibited supports to their antidiabetic activity [31].

CINNAMON EXTRACT (CE) AND CINNAMON POLYPHENOLS (CP)

CE and CP with procyanidin type-A polymers exhibit the potential to increase the amount of protein tristetraprolin (TTP), IR, and GLUT4 in mouse 3T3-L1 adipocytes. Immunoblotting showed that CP increased IR levels and that both CE and CP increased GLUT4 and TTP levels in the adipocytes. Quantitative real-time PCR indicated that CE rapidly increased TTP mRNA levels by approximately 6-fold in the adipocytes. CE at higher concentrations decreased IR protein and mRNA level. These results suggest that cinnamon exhibits the potential to increase the amount of proteins involved in insulin signaling, glucose transport, and anti-inflammatory or anti-angiogenesis response [6].

ALOE VERA

Densitometry scanning of agarose gel indicates an increase in GLUT4 transcripts by ~2.1764-fold by Aloe extract as compared to the control which is also comparable with metformin ~4.4117-fold and insulin ~3.4779-fold. *In vivo* and *in vitro* studies aqueous leaf extract of *A. vera* revealed that the glucose-lowering activities and some of its components facilitate GLUT4 mRNA expression. Up-regulation of GLUT4 mediated by stimulatory effects on the cytoskeletal proteins that help in vesicle trafficking during GLUT4 expression. The microtubule network and actin cytoskeleton by the link the signaling components or direct the vesicle movement to play a role in GLUT4 trafficking [32].

TOONA SINENSIS

Pei-Hwei *et al.*, in 2008, tested the effects of *T. sinensis* leaf extract on alloxan-induced diabetic rats. Diabetic rats had lower expressions of GLUT4, mRNA, and GLUT4 protein in brown and white adipose tissues. In contrast, diabetic rats given the extract showed a significant increase in GLUT4 mRNA and protein levels that were analyzed through the western blot and reverse transcription-PCR. Thus, the extract possesses an anti-hyperglycemic effect via an increment of insulin to mediate adipose GLUT4 [33].

MOMORDICA CHARANTIA

This is a well-reported antidiabetic plant with other pharmacological activities used in countries such as India and China. C-C. Shih *et al.*, in 2009, demonstrated that bitter melon not only influences PPAR γ -mediated pathway, which regulates adipocytokine gene expressions and also increases the numbers of GLUT4 at the cell surface, thereby promoting glucose uptake in peripheral tissue such as skeletal muscle, which is responsible for the major improvement of insulin resistance in fructose-fed rats. The extract increased the expression of PPAR γ in white adipose tissue and decreased the expression of leptin that improved insulin resistance [34].

Another study was conducted by R. Kumar *et al.*, in 2009. In this, the dose-dependent glucose uptake assay was performed on L6 myotubes. The combination of *M. charantia* with the aqueous and chloroform extracts of *M. charantia* fruit has shown the significant up-regulatory effect of GLUT4, PPAR γ , and PI3K by 3.6-, 2.8-, and 3.8-fold, respectively. The up-regulation of glucose uptake was equivalent with insulin and rosiglitazone which was roughly 2-fold over the control [10].

ABIES BALSAMEA, LARIX LARICINA, RHODODENDRON GROENLANDICUM, AND SARRACENIA PURPUREA

These plants belong to Canadian medicinal plant species which possess their hypoglycemic activity through a common mechanism similar to

that of standard drug metformin. These plants involved in the activation of AMPK-dependent pathway and alleviate insulin resistance with metabolic diseases in C2C12 murine skeletal myoblasts and H4IIE rat hepatocytes cells [35].

TAMARINDUS INDICA

The seeds of *T. indica* consist high levels of polyphenols and flavonoids. The treatment of aqueous seed extract for 4 weeks demonstrates that intracellular calcium and insulin release in isolated islets of Langerhans and improved the GLUT2 protein and SREBP-1c mRNA expression in the liver. Further, it increases GLUT4 protein and mRNA expression in the skeletal muscles of diabetic rats [36].

ISOFLAVONE FROM PTEROCARPUS MARSUPIUM

P. marsupium methanol extract activates the glucose transport in a PPAR γ mediated PI3 kinase-dependent fashion, and the *P. marsupium* isoflavone exhibits the same glucose transport activity by PPAR γ mediated through PI3 kinase-independent fashion in adipocytic cell-line 3T3-L1 [37].

CORNUS KOUSA

The leaves extract of *C. kousa* increases adipogenesis and the expression of PPAR γ in 3T3-L1 adipocytes that led to significant stimulation of glucose uptake and insulin signaling, but not to AMPK signaling [38].

PERSEA AMERICANA

The hydroalcoholic extract of the leaves of *P. americana* decreased blood glucose levels and enhanced the metabolic state of the animals. PKB activation was observed in the liver and skeletal muscle of treated rats when compared with untreated diabetic rats. This result showed that the hydroalcoholic extract regulate glucose uptake in liver and muscles through PKB/Akt activation which determined by Western blot [39].

FERMENTED TEA

Administration of fermented tea for 7 days in male ICR mice strongly proposed that activates both PI3K/Akt- and AMPK-dependent signaling pathways to enhance GLUT4 translocation. It increases the expression of IR to recover glucose intolerance [40].

PINE BARK EXTRACT

In vitro study revealed that the extract activating p38 mitogen-activated kinase which activates SGLT1 transporters. This transporter activates two different pathways of GLUT2 translocation in which an inhibitory pathway involving PI3 K mitogen-activated protein kinase or extracellular signal-regulated kinase [41].

CECROPIA OBTUSIFOLIA

Alonso-Castro *et al.*, in 2008, studied the antidiabetic mechanisms of *C. obtusifolia* aqueous extract and its active principle. It stimulating glucose uptake in insulin-sensitive and insulin-resistant adipocytes. Thus, they might act by potentiating the insulin action or by activating a signaling pathway which is parallel to the insulin pathway [42].

LYOPHYLLUM DECASTES

Miura *et al.* in explained the antidiabetic activity of *L. decastes* in KK-Ay mice, an animal model of type 2 diabetes. The extract significantly reduced the insulin resistant and improved GLUT translocation [43].

LIRIOPE PLATYPHYLLA

Homoisoflavone from this plant increased insulin-induced glucose uptake in adipocytes. This uptake was mediated through the translocation of

GLUT4 to the plasma membrane and activates IRS PI3K Akt signaling mechanism [44].

ANDROGRAPHIS PANICULATA

In vivo studies show that increased translocation of GLUT4 and α -glucosidase inhibition supports for their hypoglycemic effect which proves their multiple targets [45].

AZADIRACHTA INDICA

A. indica is an Indian medicinal plant. *In vivo* studies revealed that the hydroalcoholic extract exerted its hypoglycemic activity by increasing glucose uptake through GLUT, as well as glycogen deposition [46].

MUSA SAPIENTUM AND HELICTERES ISORA

Docking study in Autodock 4 software shows hypoglycemic activity, improve glucose uptake; flavonones activate the kinase domain in IR tyrosine kinase to *M. sapientum* [47]. *H. isora* enhance translocation of GLUT through AMP kinase cascade system [48].

In vitro, *in vivo*, and *in silico* studies investigated on various medicinal plants proves the effectiveness in the translocation of GLUT, which are summarized in Table 1.

CONCLUSION

DM and its secondary complications are due to impairment in the glucose uptake and GLUT translocation. Now, it is proven that

Table 1: Mechanism of action of medicinal plants on glucose transporters

Medicinal plant	Isolated compound/extract	Effect on GLUT
<i>Cortex cinnamomi</i>	Cinnamaldehyde	Enhancements in GLUT4 gene expression with short-term treatment in C2C12 cell line studies [16]
<i>Cinnamomum zeylanicum</i>	Cinnamaldehyde	Immunoblot analysis shows restoration of GLUT4 protein in CND. <i>In vitro</i> analysis and <i>in vivo</i> analysis proves the translocation of GLUT4 [17]
Present in many plants <i>Hippophae rhamnoides</i> sp. <i>Plumbago zeylanica</i> (root)	GA Plumbagin	GA stimulates GLUT4 translocation and glucose uptake in PKC ζ / λ dependent manner [18] One Step RT-PCR and agarose gel electrophoresis in diabetic rats proved that plumbagin improves GLUT4 mRNA expression on skeletal muscle and restores the translocation of GLUT4 in diabetic rats [19]
<i>Eucalyptus citriodora</i>	Betulonic acid and corosolic acid	Increases the GLUT4 translocation by 2.38-folds in L6 myotubes when compared with control [20]
<i>Peganum harmala</i> Linn.	4-HPA	Enhanced expression of IRS-1 mRNA. 4-HPA stimulate GLUT4 translocation through PI-3-Kinase-mediated insulin signaling pathway in 57BL/Ks-db/db mice [21]
Present in citrus fruits and tomatoes <i>Coptidis Rhizoma</i> and <i>Cortex Phellodendri</i>	Naringenin Berberine (Lee et al. 2006)	<i>In vitro</i> studies and <i>in vivo</i> studies supports antidiabetic effects of naringenin through AMPK-mediated pathway [22] Berberine increases glucose transport activity of 3T3-L1 adipocytes by enhancing GLUT1 expression and also stimulates the GLUT1-mediated glucose uptake by activating GLUT1, a result of AMPK stimulation [23]
<i>Cassia fistula</i>	Catechin	Docking study in discovery studio 2.1 shows the hypoglycemic effect by the activation of Insulin receptor and PPAR γ . Increase in both GLUT4 mRNA and protein proposes the involvement of Catechin to trigger the expression of the gene [24]
<i>Trigonella</i>	Vanadate	Trigonella treatment increases the insulin levels due to stimulation of residual beta cells in diabetic rats and vanadate being an insulin-sensitizing agent augments the action of insulin on GLUT4 translocation [25]
<i>Embelia ribes</i> Burm	Embelin	Increased the PPAR γ expression in epididymal adipose tissue. And regulated insulin-mediated glucose uptake in epididymal adipose tissue through translocation and activation of GLUT4 in PI3K/p-Akt signaling cascade [26]
CPE	EC	EC and CPE strengthen the insulin signaling by activating key proteins of that pathway and regulating glucose production through AKT and AMPK modulation in HepG2 cells [27]
<i>Panax ginseng</i> <i>Tinospora cordifolia</i>	Ginsenoside Rh2 Palmatine	Enhance GLUT4 mRNA expression in adipose tissues of diabetic rats [28] The expression of PPAR γ is up-regulated by palmatine and <i>Tinospora cordifolia</i> . Expression of PPAR γ is down regulated by palmatine and <i>Tinospora cordifolia</i> treatment. The antidiabetic activity is mediated by promoting GLUT4 expression and also moderately by up-regulating PPAR γ expression [29]
<i>Aegles marmelos</i> and <i>Syzygium cumini</i> <i>Allium sativum</i> , <i>Allium ascalonicum</i> , <i>Salvia officinalis</i>	Methanolic extract Methanolic extracts	These plants augmenting the glucose transport by up-regulation of GLUT4, PPAR γ and PI3 kinase [30] Densitometric scanning reveals that <i>Allium sativum</i> increases in Ins and GLUT4 genes transcripts by 0.57-fold and 1.21-fold than control. <i>Allium ascalonicum</i> proves the increase in Ins and GLUT4 gene 0.31, 0.71-fold, respectively. <i>In vitro</i> studies shown 0.19-fold increase in INS gene and 1.05-fold gain in GLUT4 gene expression by <i>Salvia officinalis</i> [31]
Cinnamon extract <i>Aloe vera</i>	Polyphenols Aqueous extract	Results confirmed the increased level of GLUT4 expression [32] Up-regulation of GLUT4 mediated by stimulatory effects on the cytoskeletal proteins that help in vesicle trafficking during GLUT4. The microtubule network and actin cytoskeleton other link the signaling components or direct the vesicle movement to play a role in GLUT4 trafficking [33]
<i>Toona sinensis</i>	Leaf extract	Increases glucose uptake in the 3T3-L1 adipocytes and mediates the GLUT4 translocation mechanism [34]
<i>Momordica charantia</i>	Fruit extract	Increases the expression of PPAR γ in white adipose tissue. Increases the mRNA expression and protein of GLUT4 in skeletal muscle [34,10]

(Contd.....)

Table 1: (Contd...)

Medicinal plant	Isolated compound/extract	Effect on GLUT
<i>Abies balsamea</i> , <i>Alnus incana</i> <i>Clausen</i> , <i>Larix laricina</i> <i>Picea mariana</i> , <i>Pinus banksiana</i> , <i>Rhododendron groenlandicum</i> , <i>Sarracenia purpurea</i> L., <i>Sorbus decora</i> Schneid <i>Tamarindus indica</i>	Aqueous seed extract	Glucose uptake in C2C12 skeletal muscle increased by these plants through AMPK signaling pathway in 18 hrs of treatment. Phosphorylation of AMPK and ACC were increased up to 2.5- and 3.5-fold, respectively. The AMPK Pathway converges with the insulin receptor pathway at the level of AS160 and in this way can induce the translocation of GLUT4 GLUTs to the sarcolemma and promote an increase in the rate of uptake [35] Quantitative reverse transcription-PCR results showed increase in muscle GLUT4 mRNA and liver SREBP-1c mRNA concentrations of diabetic treated rats [36]
<i>Pterocarpus marsupium</i>	Isoflavone	Isoflavone of this plant exert the same glucose transport activity in an alternate mechanism; PPAR mediated by PI3 kinase-independent manner in adipocytic cell-line 3T3-L1 [37]
<i>Cornus kousa</i>		Results showed that increases the GLUT4 translocation through increased insulin signaling of 3T3-L1 adipocytes [38]
<i>Persea americana</i>	Hydroalcoholic extract	The extract regulates glucose uptake in liver and muscles by the activation of PKB/Akt [39]
Fermented tea extract		It activates both PI3K/Akt- and MPK-dependent signaling pathways to induce GLUT4 translocation and increases the expression of insulin receptor to improve glucose intolerance [40]
Pine bark extract		<i>In vitro</i> the results proved that the extract acts by activating p38 mitogen-activated kinase, which in turn activates SGLT1 transporters [41]
<i>Cecropia obtusifolia</i>	Aqueous extract	Activates the insulin signaling pathway and translocate GLUTs [42]
<i>Lyophyllum decastes</i>	Aqueous extract	Increases the translocation of GLUT4 in the plasma membrane [43]
<i>Liriope platyphylla</i>	Homoisoflavone	Stimulates IRS - phosphatidylinositol 3 kinase-Akt signaling mechanism [44]
<i>Andrographis paniculata</i>	andrographolide	<i>In vivo</i> studies show higher expression of GLUT4 [45]
<i>Azadirachta indica</i>	Hydroalcoholic extract	Increases the glucose uptake through cascade events in adipose and skeletal tissues [46]
<i>Musa sapientum</i>		Docking study in Autodock 4 software shows hypoglycemic activity; improve glucose uptake; Flavonones activate the kinase domain in insulin receptor tyrosine kinase [47]
<i>Helicteres isora</i>	Fruits	Docking studies in Autodock 4 show potent antidiabetic activity against type 2 diabetes mellitus through drug action on AMP kinase cascade system [48]

GLUT: Glucose transporter, GA: Galli acid, CND: Cinnamaldehyde, PCR: Polymerase chain reaction, mRNA: Messenger RNA, 4-HPA: 4-hydroxyphenylacetic acid, IRS: Insulin receptor substrate-1, AMPK: AMP-activated protein kinase, PPAR γ : Peroxisome proliferator-activated receptor-gamma, CPE: Cocoa phenolic extract, EC: Epicatechin

traditional antidiabetic medicinal plants and their active constituents could enhance the GLUT translocation from an intracellular pool to the plasma membrane through signaling pathways. These plants could be used as efficient therapeutic agents with less harmful side effects and cost effective than synthetic drugs for controlling glucose homeostasis. There is an increasing evidence from the data reviewed in the current article suggests that the translocation of GLUT which can revive DM, therefore, may lead to the discovery of the next generation of antidiabetic drugs.

ACKNOWLEDGMENT

The authors would like to thank the management of VIT University for supporting the study.

REFERENCES

- Haddad PS, Musallam L, Martineau LC, Harris C, Lavoie L, Arnason JT, et al. Comprehensive evidence-based assessment and prioritization of potential antidiabetic medicinal plants: A case study from Canadian eastern James Bay Cree traditional medicine. *Evid Based Complement Alternat Med* 2012;2012:893426.
- Pandey A, Tripathi P, Pandey R, Srivastava R, Goswami S. Alternative therapies useful in the management of diabetes: A systematic review. *J Pharm Bioallied Sci* 2011;3(2):504-12.
- Modak M, Dixit P, Londhe J, Ghaskadbi S, Devasagayam TP. Indian herbs and herbal drugs used for the treatment of diabetes. *J Clin Biochem Nutr* 2007;40(3):163-73.
- Wang Z, Wang J, Chan P. Treating type 2 diabetes mellitus with traditional Chinese and Indian medicinal herbs. *Evid Based Complement Alternat Med* 2013;2013:343594.
- Alarcon-Aguilara FJ, Roman-Ramos R, Perez-Gutierrez S, Aguilar-Contreras A, Contreras-Weber CC, Flores-Saenz JL. Study of the anti-hyperglycemic effect of plants used as antidiabetics. *J Ethnopharmacol* 1998;61(2):101-10.
- Cao H, Polansky MM, Anderson RA. Cinnamon extract and polyphenols affect the expression of tristetraprolin, insulin receptor, and glucose transporter 4 in mouse 3T3-L1 adipocytes. *Arch Biochem Biophys* 2007;459(2):214-22.
- Pannangpetch P, Taejarernwiriyaikul O, Kongyingyoes B. P-145 Ethanol extract of *Combretum decandrum* Roxb. Decreases blood glucose level and oxidative damage in streptozotocin-induced diabetic rats. *Diabetes Res Clin Pract* 2008;79:S1-127.
- Cazarolli LH, Folador P, Moresco HH, Brighente IM, Pizzolatti MG, Silva FR. Mechanism of action of the stimulatory effect of apigenin-6-C-(2''-O-alpha-L-rhamnopyranosyl)-beta-L-fucopyranoside on 14C-glucose uptake. *Chem Biol Interact* 2009;179(2-3):407-12.
- Chen X, Bai X, Liu Y, Tian L, Zhou J, Zhou Q, et al. Anti-diabetic effects of water extract and crude polysaccharides from tuberous root of *Liriope spicata* var. *prolifera* in mice. *J Ethnopharmacol* 2009;122(2):205-9.
- Kumar R, Balaji S, Uma TS, Sehgal PK. Fruit extracts of *Momordica charantia* potentiate glucose uptake and up-regulate Glut-4, PPAR gamma and PI3K. *J Ethnopharmacol* 2009;126(3):533-7.
- Jiang CS, Liang LF, Guo YW. Natural products possessing protein tyrosine phosphatase 1B (PTP1B) inhibitory activity found in the last decades. *Acta Pharmacol Sin* 2012;33(10):1217-45.
- Iseli TJ, Turner N, Zeng XY, Cooney GJ, Kraegen EW, Yao S, et al. Activation of AMPK by bitter melon triterpenoids involves CaMKK β . *PLoS One* 2013;8:e62309.
- El-Abhar HS, Schaalan MF. Phytotherapy in diabetes: Review on potential mechanistic perspectives. *World J Diabetes* 2014;5(2):176-97.
- Gould GW, Holman GD. The glucose transporter family: Structure, function and tissue-specific expression. *Biochem J* 1993;295:329-41.
- Garvey WT, Maianu L, Huecksteadt TP, Birnbaum MJ, Molina JM, Ciaraldi TP. Pretranslational suppression of a glucose transporter protein causes insulin resistance in adipocytes from patients with non-insulin-dependent diabetes mellitus and obesity. *J Clin Invest* 1991;87(3):1072-81.
- Nikzamid A, Palangi A, Kheirollaha A, Tabar H, Malakaskar A, Shahbazian H, et al. Expression of glucose transporter 4 (GLUT4) is

- increased by cinnamaldehyde in C2C12 mouse muscle cells. Iran Red Crescent Med J 2014;16(2):e13426.
17. Anand P, Murali KY, Tandon V, Murthy PS, Chandra R. Insulinotropic effect of cinnamaldehyde on transcriptional regulation of pyruvate kinase, phosphoenolpyruvate carboxykinase, and GLUT4 translocation in experimental diabetic rats. Chem Biol Interact 2010;186(1):72-81.
 18. Prasad CN, Anjana T, Banerji A, Gopalakrishnapillai A. Gallic acid induces GLUT4 translocation and glucose uptake activity in 3T3-L1 cells. FEBS Lett 2010;584(3):531-6.
 19. Sunil C, Duraipandiyan V, Agastian P, Ignacimuthu S. Antidiabetic effect of plumbagin isolated from *Plumbago zeylanica* L. root and its effect on GLUT4 translocation in streptozotocin-induced diabetic rats. Food Chem Toxicol 2012;50(12):4356-63.
 20. Wang C, Yang J, Zhao P, Zhou Q, Mei Z, Yang G, et al. Chemical constituents from *Eucalyptus citriodora* hook leaves and their glucose transporter 4 translocation activities. Bioorg Med Chem Lett 2014;24(14):3096-9.
 21. Naresh G, Jaiswal N, Sukanya P, Srivastava AK, Tamrakar AK, Narender T. Glucose uptake stimulatory effect of 4-hydroxypipercolic acid by increased GLUT 4 translocation in skeletal muscle cells. Bioorg Med Chem Lett 2012;22(17):5648-51.
 22. Zygmunt K, Faubert B, MacNeil J, Tsiani E. Naringenin, a citrus flavonoid, increases muscle cell glucose uptake via AMPK. Biochem Biophys Res Commun 2010;398:178-83.
 23. Lee YS, Kim WS, Kim KH, Yoon MJ, Cho HJ, Shen Y, et al. Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states. Diabetes 2006;55(8):2256-64.
 24. Pitchai D, Manikkam R. Hypoglycemic and insulin mimetic impact of catechin isolated from *Cassia fistula*: A substantiate *In silico* approach through docking analysis. Med Chem Res 2012;21:2238-50.
 25. Mohammad S, Taha A, Bamezai RN, Baquer NZ. Modulation of glucose transporter (GLUT4) by vanadate and *Trigonella* in alloxan-diabetic rats. Life Sci 2006;78(1):820-4.
 26. Gandhi GR, Stalin A, Balakrishna K, Ignacimuthu S, Paulraj MG, Vishal R. Insulin sensitization via partial agonism of PPAR γ and glucose uptake through translocation and activation of GLUT4 in PI3K/p-Akt signaling pathway by embelin in type 2 diabetic rats. Biochim Biophys Acta 2013;1830(1):2243-55.
 27. Cordero-Herrera I, Martín MA, Bravo L, Goya L, Ramos S. Cocoa flavonoids improve insulin signalling and modulate glucose production via AKT and AMPK in HepG2 cells. Mol Nutr Food Res 2013;57(9):974-85.
 28. Lai DM, Tu YK, Liu IM, Chen PF, Cheng JT. Mediation of beta-endorphin by ginsenoside Rh2 to lower plasma glucose in streptozotocin-induced diabetic rats. Planta Med 2006;72(1):9-13.
 29. Sangeetha MK, Priya CD, Vasanthi HR. Anti-diabetic property of *Tinospora cordifolia* and its active compound is mediated through the expression of Glut-4 in L6 myotubes. Phytomedicine 2013;20(3-4):246-8.
 30. Anandharajan R, Jaiganesh S, Shankernarayanan NP, Viswakarma RA, Balakrishnan A. *In vitro* glucose uptake activity of *Aegles marmelos* and *Syzygium cumini* by activation of Glut-4, PI3 kinase and PPAR γ in L6 myotubes. Phytomedicine 2006;13:434-41.
 31. Noipha K, Ratanachaiyavong S, Ninla-Aesong P. Enhancement of glucose transport by selected plant foods in muscle cell line L6. Diabetes Res Clin Pract 2010;89(2):e22-6.
 32. Kumar R, Sharma B, Tomar NR, Roy P, Gupta AK, Kumar A. *In vivo* evaluation of hypoglycemic activity of *Aloe* spp. and identification of its mode of action on GLUT-4 gene expression *in vitro*. Appl Biochem Biotechnol 2011;164(8):1246-56.
 33. Wang PH, Tsai MJ, Hsu CY, Wang CY, Hsu HK, Weng CF. *Toona sinensis* Roem (Meliaceae) leaf extract alleviates hyperglycemia via altering adipose glucose transporter 4. Food Chem Toxicol 2008;46(7):2554-60.
 34. Shih CC, Lin CH, Lin WL, Wu JB. *Momordica charantia* extract on insulin resistance and the skeletal muscle GLUT4 protein in fructose-fed rats. J Ethnopharmacol 2009;123(1):82-90.
 35. Martineau LC, Adeyiwola-Spoor DC, Vallerand D, Afshar A, Arnason JT, Haddad PS. Enhancement of muscle cell glucose uptake by medicinal plant species of Canada's native populations is mediated by a common, metformin-like mechanism. J Ethnopharmacol 2010;127(2):396-406.
 36. Sole SS, Srinivasan BP. Aqueous extract of tamarind seeds selectively increases glucose transporter-2, glucose transporter-4, and islets' intracellular calcium levels and stimulates β -cell proliferation resulting in improved glucose homeostasis in rats with streptozotocin-induced diabetes mellitus. Nutr Res 2012;32(8):626-36.
 37. Anandharajan R, Pathmanathan K, Shankernarayanan NP, Vishwakarma RA, Balakrishnan A. Upregulation of Glut-4 and PPAR γ by an isoflavone from *Pterocarpus marsupium* on L6 myotubes: A possible mechanism of action. J Ethnopharmacol 2005;97(2):253-60.
 38. Kim D, Park KK, Lee SK, Hwang JK. *Cornus kousa* F. Buerger ex Miquel increases glucose uptake through activation of peroxisome proliferator-activated receptor γ and insulin sensitization. J Ethnopharmacol 2011;133(2):803-9.
 39. Lima CR, Vasconcelos CF, Costa-Silva JH, Maranhão CA, Costa J, Batista TM, et al. Anti-diabetic activity of extract from *Persea americana* Mill. Leaf via the activation of protein kinase B (PKB/Akt) in streptozotocin-induced diabetic rats. J Ethnopharmacol 2012;141(1):517-25.
 40. Yamashita Y, Wang L, Tinshun Z, Nakamura T, Ashida H. Fermented tea improves glucose intolerance in mice by enhancing translocation of glucose transporter 4 in skeletal muscle. J Agric Food Chem 2012;60(45):11366-71.
 41. El-Zein O, Kreydiyyeh SI. Pine bark extract inhibits glucose transport in enterocytes via mitogen-activated kinase and phosphoinositol 3-kinase. Nutrition 2011;27(6):707-12.
 42. Alonso-Castro AJ, Miranda-Torres AC, González-Chávez MM, Salazar-Olivo LA. *Cecropia obtusifolia* Bertol and its active compound, chlorogenic acid, stimulate 2-NBDglucose uptake in both insulin-sensitive and insulin-resistant 3T3 adipocytes. J Ethnopharmacol 2008;120(3):458-64.
 43. Miura T, Kubo M, Itoh Y, Iwamoto N, Kato M, Park SR, et al. Antidiabetic activity of *Lyophyllum decastes* in genetically type 2 diabetic mice. Biol Pharm Bull 2002;25(9):1234-7.
 44. Choi SB, Wha JD, Park S. The insulin sensitizing effect of homoisoflavone-enriched fraction in *Liriope platyphylla* Wang et Tang via PI3-kinase pathway. Life Sci 2004;75(22):2653-64.
 45. Yu BC, Hung CR, Chen WC, Cheng JT. Antihyperglycemic effect of andrographolide in streptozotocin-induced diabetic rats. Planta Med 2003;69(12):1075-9.
 46. Chattopadhyay RR. Possible mechanism of antihyperglycemic effect of *Azadirachta indica* leaf extract. Part IV. Gen Pharmacol 1996;27(3):431-4.
 47. Ganugapati J, Baldwa A, Lalani S. Molecular docking studies of banana flower flavonoids as insulin receptor tyrosine kinase activators as a cure for diabetes mellitus. Bioinformation 2012;8(5):216-20.
 48. Vennila S, Bupesh G, Saravanamurali K, SenthilKumar V, SenthilRaja R, Saran N1, et al. *In silico* docking study of compounds elucidated from *Helicteres isora* fruits with ampk kinase - Insulin receptor. Bioinformation 2014;10(5):263-6.